> utility and (2) share a substantial structural feature disclosed as being essential to that utility.

(Paper No. 9, page 3 (quoting M.P.E.P. § 803.02, second paragraph).)

Applicants note that M.P.E.P. § 803.02 is directed to restriction of subject matter presented in Markush groups. Applicants also note that the portion of M.P.E.P. § 803.02 which immediately precedes the text quoted by the Examiner reads as follows:

> If the members of the Markush group are sufficiently few in number *or* so closely related that a search and examination of the entire claim can be made without serious burden, the examiner *must* examine all claims on the merits, even though they are directed to independent and distinct inventions. *In such a case, the examiner will not follow the procedure described below and will not require restriction.*

(M.P.E.P. § 803.02, first paragraph (emphases added).) Applicants point out that all of the members of the Markush groups in the claims which the Examiner has objected to are closely related (*i.e.*, are directed to nucleic acids which encode amino acid sequences shown in SEQ ID NOs:2 and 4). Thus, a search of the subject matter of claims 57, 62-70, 73-81 and 94-100 would not place a "serious burden" on the Examiner. In fact, as evidenced by the rejection of claims 27-119 under 35 U.S.C. § 102(b) discussed below, the Examiner appears to have already performed a search of the subject matter of claims 57, 62-70, 73-81 and 94-100.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the objection to claims 57, 62-70, 73-81 and 94-100.

II. The Rejection of Claims 27-119 Under 35 U.S.C. § 101

The Examiner has rejected claims 27-119 of the captioned application under 35 U.S.C. § 101, on the basis that "they are drawn to an invention with no apparent or disclosed specific and substantial credible utility." (Paper No. 9, page 3.) In particular, the Examiner asserts that, "[t]he

instant application does not disclose the biological role of . . . [the described] protein or its significance." (Paper No. 9, page 3.) As explained below, Applicants respectfully disagree.

Applicants begin by emphasizing that, contrary to the Examiner's contention, the specification does indeed disclose "function or biological significance [of the claimed DR3-receptor][1] beyond the fact that it belongs to the TNF receptor family." (*See* Paper No. 9, page 5.) Moreover, in this light, it is apparent that the instant case is not directly analogous to situation in *Brenner v. Manson*, 148 U.S.P.Q. 689 (U.S. 1966), in contrast to the Examiner's assertion. (*See* Paper No. 9, page 4.)

In *Brenner*, the issue was not whether a disclosed utility was sufficient, because the applicant was trying to establish an earlier date of invention for the purpose of provoking an interference. *Brenner*, 148 U.S.P.Q. at 690. The issue in *Brenner* was whether the applicant had made an adequate "showing" to establish a prior date of invention (*i.e.*, whether "the process claim has been reduced to production of a product shown to be useful, . . ." through actual demonstration of the utility). *Brenner*, 148 U.S.P.Q. at 695. The only evidence that the applicant had to make this "demonstration" was a reference to an article by a third party showing the activity of an adjacent homologue of the subject steroid compound. *Brenner*, 148 U.S.P.Q. at 694. The applicant had done nothing to show or demonstrate that the compound was indeed useful. *See Brenner*, 148 U.S.P.Q. at 694. Indeed, the examiner's initial basis for refusing to declare an interference was that the applicant had failed to disclose any utility at all. *Brenner*, 148 U.S.P.Q. at 690. Thus, the rejection of the request for declaration of an interference was upheld. *Brenner*, 148 U.S.P.Q. at 698.

In contrast, the issue in the present case is whether the instant application explicitly teaches at least one utility which meets the requirements of 35 U.S.C. § 101. In this regard, Applicants note

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[1]While the claims of the captioned application are directed to nucleic acids, Applicants have chosen to discuss herein utilities related to the polypeptide expression products of these nucleic acids, but reserve the right to assert that nucleic acids of the invention have practical utility regardless of whether they encode DR3-receptor polypeptides.

that the captioned application clearly indicates that DR3-receptors have specific utilities. For example, the captioned application indicates that DR3-receptors induce apoptosis. (Specification, *inter alia*, page 38, lines 5-13; and page 39, lines 3-7.) The accuracy of these assertions is confirmed by data provided in Example 6 of the captioned application which, as the Examiner clearly recognizes, teaches that "over expression of this putative receptor in a cell mimics ligand activation of this receptor and that this receptor activation induces cell death. . . ." (Paper No. 9, page 4.)

Further, the captioned application states that:

> The experiments set forth in Example[] 6 . . . demonstrate that DR3 is a death domain-containing molecule capable of triggering both apoptosis and NF-kB activation, two pathways dominant in the regulation of the immune system. . . . In addition, the experiments set forth below demonstrate that DR3-induced apoptosis was blocked by the inhibitors of ICE-like proteases, CrmA and z-VAD-fmk. Importantly, apoptosis induced by DR3 was also blocked by dominant negative versions of FADD (FADD-DN) or FLICE (FLICE-DN/MACHa1C360S), which were previously shown to inhibit death signaling by Fas/APO-1 and TNFR-1. Thus, inhibitors of ICE-like proteases, FADD-DN and FLICE-DN/MACHa1C360S could also be used as antagonists for DR3 activity.

(Specification, page 43, line 23, to page 44, line 5.) The captioned application also states that, "[d]iseases associated with increased cell survival, or the inhibition of apoptosis, include cancers, autoimmune disorders, viral infections, inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. . . ." (Specification, page 5, lines 23-26.) Thus, in contrast to the Examiner's assertion, "function or biological significance" of the claimed DR3-receptors is indeed disclosed in the specification. Moreover, the utilities cited above are certainly specific and substantial. Applicants respectfully emphasize the well settled law that only one utility needs to be established to fulfill the requirements of 35 U.S.C. §§ 101 and 112. *See Raytheon v. Roper*, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984); M.P.E.P. § 2107.01; and Revised Interim Utility Guidelines Training Materials (Utility Guidelines), page 3.

Moreover, the disclosed utilities are credible. Applicants note that the manner of making and using an invention disclosed in a specification must be accepted by the PTO "unless there is reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971); *see* Utility Guidelines, page 5. In applying this rule to the utility requirement, the Federal Circuit held:

> the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

In re Brana, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (citations omitted). The Examiner has not made the required showing that the disclosed, specific and substantial utilities for polypeptides encoded by the claimed nucleic acids cited above would not be credible in light of the teachings of the specification. Given the detailed description of the structure and activity of the specified polypeptides and the disclosed homology to other members of the TNF receptor family (see Figure 3 of the captioned application), one skilled in the art would have found the asserted utilities for the claimed DR3-receptor nucleic acids credible upon reading the specification.

Nonetheless, in order to obviate the rejection, Applicants submit herewith documentary evidence further demonstrating that the cited utilities are indeed credible. The Federal Circuit has set forth the standard by which an asserted utility is established through supporting data. First, the Federal Circuit pointed out that its "predecessor court has noted that adequate proof of any pharmacological activity constitutes a showing of practical utility." *Cross v. Izuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985) (citing *Nelson v. Bowler*, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980) and *Rey-Bellet v. Englehardt*, 181 U.S.P.Q. 453, 454 (C.C.P.A. 1974)). Specifically, the Federal Circuit held:

> based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where

> the disclosure of a pharmacological activity is reasonably based upon the probative evidence.

Cross, 224 U.S.P.Q. at 747 (citations omitted). With the above in mind, Applicants respectfully direct the Examiner's attention to Chinnaiyan *et al.*, *Science, 274*:990-992 (1996) [Exhibit A], as well as to Example 6 of the captioned application.

Clearly the activities reported in Chinnaiyan *et al.* [Exhibit A] and Example 6, demonstrate that polypeptides encoded by the claimed nucleic acids induce apoptosis and, thus, would be useful, for example, for treating "[d]iseases associated with increased cell survival, or the inhibition of apoptosis, . . ." (Specification, page 5, lines 23-24.)

Applicants note that Chinnaiyan *et al.* report data which is contained in Example 6 of the captioned application. Thus, as evidenced by a peer reviewed publication (*i.e.*, Chinnaiyan *et al.*), data contained in the specification has been found credible by those skilled in the art.

Moreover, the information cited above sufficiently "rebuts the basis or logic" of the Examiner's rejection. Utility Guidelines, page 5. Thus, the claimed nucleic acids have proven *in vitro* pharmacological activity that is reasonably correlated to an asserted *in vivo* utility. Therefore, the claimed compounds have a utility that is disclosed in the specification. Applicants assert that no more is needed to satisfy the utility requirement.

The Examiner appears to base the rejection of claims 27-119 for lack of utility on a series of statements. Applicants address two of these statements below.

A. "The instant claims are drawn to an isolated nucleic acid encoding a protein of as yet undetermined function or biological significance beyond the fact that it belongs to the TNF receptor family. . . ."[2]

The Examiner appears to assert that Applicants have merely discovered a nucleic acid which encodes yet another member of the TNF receptor family. Assuming solely for the sake or argument that all TNF receptors were to share identical functional activities, Applicants point out that

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[2]Paper No. 9, page 5.

DR3-receptors of the invention would have practical utility under the Utility Guidelines. In support of Applicants' position, the Examiner's attention is drawn to Example 10 of the Utility Guidelines. (Utility Guidelines, pages 53-55.) In particular, the DNA fragment described in Example 10 encodes a polypeptide identified as a DNA ligase *solely* on the basis of homology with known ligases. Example 10 states that, under the particular circumstances, a rejection of the exemplified claim should not be made under 35 U.S.C. § 101. (Utility Guidelines, page 55.) Applicants point out that Example 10 does not indicate that the exemplified claim should be rejected on the basis that ligation activity is an inherent property of all DNA ligases. Further, such an application of the utility requirement would render most nucleic acids and polypeptides unpatentable regardless of how well characterized these molecules were at the time of filing. Applicants do not believe that such a result is the intention of the Utility Guidelines or comports with the current state of the law.

Applicants again note that they have identified specific functional characteristics of DR3-receptors of the invention (*e.g.*, the ability to induce apoptosis upon overexpression). In other words, the specific functional characteristics of DR3-receptors of the invention are not functional activities which are associated with all proteins.

B. "There is little doubt that, after complete characterization, this protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. . . ."[3]

The Examiner appears to assert that Applicants have not characterized DR3-receptors sufficiently to demonstrate that they have specific, substantial, and credible utility. Applicants respectfully disagree.

Applicants have characterized DR3-receptors as death domain containing receptors involved in apoptosis. Further, as already noted, the data provided in Example 6 of the captioned application

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[3]Paper No. 9, page 5.

confirms that DR3-receptors are involved in apoptosis. Applicants point out that less data is provided in the fact pattern presented in Example 10 of the Utility Guidelines, yet these Guidelines indicate that a rejection of the exemplified claim should not be made under 35 U.S.C. § 101. (Utility Guidelines, page 55.)

In view of the comments set out above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-119 under 35 U.S.C. § 101.

III. The Rejection of the Claims under 35 U.S.C. § 112, First Paragraph

A. Claims 27-119

The Examiner has rejected claims 27-119 of the captioned application under 35 U.S.C. § 112, first paragraph, "as failing to adequately teach how to use the instant invention for those reasons given above with regard to the rejection of these claims under 35 U.S.C. § 101." (Paper No. 9, page 6.) Applicants respectfully disagree and note that this rejection has been addressed above with regard to the rejection of these claims under 35 U.S.C. § 101.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-119 under 35 U.S.C. § 112, first paragraph.

B. Claims 43-56

The Examiner has rejected claims 43-56 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention." (Paper No. 9, page 6.)

The Examiner asserts that, "[claims 43-56] expressly require the biological material recited therein . . . ." (Paper No. 9, page 6.) The Examiner further asserts, in essence, that this rejection can be overcome if Applicants, their assignee, or their agent provide a declaration averring that the

"deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure . . . **and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent**." (Paper No. 9, pages 6-7.) A Declaration for Deposited Biological Materials signed by an attorney of record which meets the conditions referred to by the Examiner is submitted herewith.

The Examiner also asserts that, "the deposit must be referred to in the body of the specification and be identified by deposit (accession number) number, name and address of the depository, and the complete taxonomic description." (Paper No. 9, page 7.)

Applicants note that the specification, at page 8, lines 5-10, reads, in relevant part, as follows:

> The nucleotide sequence shown in FIG. 2 [SEQ ID NO:3] was obtained by sequencing a clone obtained from a HUVEC library, which was deposited on October 10, 1996 at the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA, and given Accession Number 97757. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, LaJolla, CA).[4]

In view of the above, Applicants point out that the specification of the captioned application contains the information referred to by the Examiner.

In view of the submission herewith of the Declaration for Deposited Biological Materials and the above remarks, it is respectfully submitted that the Examiner's positions regarding the biological deposit are moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 43-56 under 35 U.S.C. § 112, first paragraph.

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[4]The text of the captioned application set out here was amended by the Preliminary Amendment filed May 19, 1999 to refer to the new address of the American Type Culture Collection. These amendments have been incorporated into the text shown here.

IV. The Rejection of Claims 42, 56, 69, 80, 101, 110 and 119 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 42, 56, 69, 80, 101, 110 and 119 of the captioned application under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Paper No. 9, page 7.) In particular, the Examiner asserts that "[t]hese claims are vague and indefinite because the identity of the polypeptide being produced by the claimed method is unclear." (Paper No. 9, page 7.)

While Applicants respectfully disagree with the Examiner, claims 42, 56, 69, 80, 101, 110 and 119 have been amended herein to clarify the subject matter which Applicants regard as the invention.

In view of the amendments to claims 42, 56, 69, 80, 101, 110 and 119 submitted herein, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejection of these claims under 35 U.S.C. § 112, second paragraph.

V. The Rejection of Claims 27-119 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 27-119 of the captioned application under 35 U.S.C. § 102(b) as anticipated by Kitson *et al.*, *Nature 384*:372-375 (1996). (Paper No. 9, page 8.) The Examiner bases this rejection on the position that, "[b]ecause of the rejection of these claims for lack of utility under the first paragraph of 35 USC 112 above, the instant application does not receive benefit under 35 USC 120 from any prior applications." (Paper No. 9, page 8.)

In order for a printed publication to render a claim unpatentable under 35 U.S.C. § 102(b), the document must have been published "more than one year prior to the date of the application for

patent . . . ." 35 U.S.C. § 102(b); *see also Woodland Trust v. Flowertree Nursery Inc.*, 47 U.S.P.Q.2d 1363, 1365 (Fed. Cir. 1998).

Applicants note that Kitson *et al.* appears to have published in November of 1996. Further, the captioned application is a continuation of U.S. Application No. 08/815,469 ('469 application), filed March 11, 1997. Thus, the disclosure of the '469 application is the same as the disclosure of the captioned application. Furthermore, the claims pending in the captioned application are supported by U.S. Application No. 60/028,711, filed October 17, 1996. Thus, Kitson *et al.* is not prior art with respect to the pending claims.

Applicants assert that claims 27-119 are supported by the '469 application, for the same reasons that the captioned application supports these claims. In other words, Applicants assert that the utility requirement is satisfied for claims 27-119 based on the disclosures of both the '469 application and the captioned application. Thus, claims 27-119 are entitled to the benefit of the filing date of the '469 application and Kitson *et al.* is not properly citable under 35 U.S.C. § 102(b) against these claims.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejection of claims 27-119 under 35 U.S.C. § 102(b).

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider the outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition

for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 202-789-5509.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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